The harms of early cessation of trials on systematic reviews

Elsevier Editorial System(tm) for The Lancet Gastroenterology & Hepatology
Manuscript Draft

Manuscript Number: THELANCETGASTROHEP-D-19-00242

Title: Influence of early cessation of clinical trials in surgery for harm on subsequent systematic reviews and meta-analyses

Article Type: Correspondence

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Manuscript Region of Origin: UNITED KINGDOM

Influence of early cessation of clinical trials in surgery for harm on subsequent systematic reviews and meta-analyses

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Randomised controlled trials form an important part of the evidence supporting surgical innovation. The Leopard-2 trial of laparoscopic versus open pancreatoduodenectomy for pancreatic or periampullary cancer was stopped early due to safety concerns when it became clear that after randomisation of 99 patients proceeding to surgery there was a 5 fold increase in 90 day mortality in the laparoscopic surgery arm[1].

We are interested in the consequences of the early termination of clinical trials for subsequent systematic reviews and meta-analyses. Clearly the early cessation of a trial on safety grounds is justifiable, however, it creates an interesting problem in interpretation. It could be presumed that had the Leopard 2 trial been allowed to continue it might have shown an adverse effect of laparoscopic pancreatoduodenectomy that would have had statistical power. Clearly this would have been at a human cost and so is unacceptable.

Researchers studying the question of equivalence or superiority of laparoscopic or open pancreatoduodenectomy are likely to pool data from the Leopard 2 trial into meta-analyses and there is no specific guidance about how to handle such data. The PRISMA statement[2] describes the need to describe sources of potential bias in the methodology or results presentation of clinical trials but does not specifically comment on the issue of early cessation of clinical trials due to adverse or unfavourable outcomes.

Trials which are stopped early following analysis of interim data are likely to show more extreme intervention effects than those which enroll their intended sample size particularly in trials with rare events[3,4]. Further trials investigating the same hypothesis are unlikely to replicate the extreme point estimate obtained in the truncated trial, a feature known as “regression to the truth”. Whilst much of the existing debate over the influence of truncated trials has focused on inappropriate adoption of novel treatments following truncated trials demonstrating benefit[5], trials stopped early for harm are subject to the same biases. Researchers, clinicians and policy-makers will undoubtedly make decisions, which incorporate evidence from truncated trials, such as the Leopard 2 trial, which raise ethical and practical concerns about how such trials are interpreted. Potential implications of decisions made on the basis of results from the Leopard 2 trial include misleading summary effects from meta-analyses, a potential “freezing” effect on the conduct of similar trials and interpretation of the large effect size as irrefutable evidence of harm despite a lack of statistical significance or data available from other trials.

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